
A novel profibrotic mechanism mediated by TGFbeta-stimulated collagen prolyl hydroxylase expression in fibrotic lung mesenchymal cells.

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Public Summary:

Scientific Abstract:

Idiopathic pulmonary fibrosis is a severe chronic lung disease with a high mortality rate. Excessive TGFbeta signalling is recognized as a central player in lung fibrosis. However, the related mechanisms remain unclear. Herein we used a novel Tbx4 lung enhancer-driven Tet-On transgenic system to inhibit TGFbeta signalling in mouse lung-resident mesenchymal cells at different stages of bleomycin-induced fibrosis, by conditionally knocking out TGFbeta receptor II or expressing a dominant-negative TGFbeta receptor II. Abrogation of mesenchymal TGFbeta signalling markedly attenuated bleomycin-induced fibrotic pathology, which was independent of altered early inflammation. Furthermore, a novel TGFbeta downstream target gene P4HA3 (an alpha-subunit of collagen prolyl hydroxylase) was identified, and its expression was significantly increased in fibroblastic foci of both bleomycin-induced fibrotic mouse lungs and idiopathic pulmonary fibrosis patients' lungs. The relationship between activated TGFbeta signalling, up-regulation of P4HA3 and increased hydroxyproline/collagen production was further verified in cultured lung fibroblasts. Moreover, inhibition of collagen prolyl hydroxylase by pyridine-2,5-dicarboxylate attenuated TGFbeta-stimulated collagen production in both cultured fibroblasts and bleomycin-induced mouse lung fibrosis. These data indicate that increased expression and activity of collagen prolyl hydroxylase is one of the important mechanisms underlying TGFbeta-mediated profibrotic effects. Inhibition of collagen prolyl hydroxylase may be a new, promising approach for preventing and treating pulmonary fibrosis.

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